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IMPROVED SCALES FOR METAL ION SOFTNESS AND TOXICITY

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Abstract—Ten scales relating to chemical hardness or softness of metal ions were compiled. These included eight published scales such as those of Pearson, Ahrland, Klopman, and Misono. Another scale consisted of the logs of the solubility products of metal sulfides, and yet another was a consensus scale constructed from $-\log K$ values for metal ion binding to seven soft ligands. These 10 scales were normalized and averaged. The resulting consensus scale for softness (σ_{Con}) appeared to be superior to any of the 10 scales used in its construction based on correlations among the scales. Other possible indicators of softness were examined, including the standard electrode potential (E^0) and the bulk metal density (ρ_{Metal}), both of which were also superior to most of the 10 scales just mentioned. Vales for σ_{Con} may be computed from E^0, ρ_{Metal}, and the first ionization potential (I_P), $R^2 = 0.867$, for the equation $\sigma_{Con} = aE^0I_P + b\rho_{Metal}$. A consensus scale for toxicity (T_{Con}) derived from studies with many different taxa correlated well ($R^2 = 0.807$) with σ_{Con} computed from the preceding equation, but incorporation of ion charge (Z) into the following equation, $T_{Con} = a\sigma_{Con} + b\sigma_{Con}Z + cZ$, increased R^2 to 0.923. Substitution of other softness scales for σ_{Con} into equations to predict T_{Con} reduced the value of R^2. Thus, σ_{Con} appears to be a superior scale for metal ion softness and toxicity, the latter being an interactive function of both softness and charge.

Keywords—Hardness Metal ion Softness Toxicity

INTRODUCTION

Quantitative scales for metal ion hardness or softness were developed in the 1960s and subsequently, following earlier classification of ions into groups according to chemical lore accumulated for a century or more [1]. The groupings known as A and B came to be designated hard and soft, respectively, by Pearson [2], who specified a borderline class as well.

In general terms, hard and soft suggest greater or lesser resistance to deformation in response to a force—electric forces in the present case. Thus, hard ions have greater resistance to deformation of the electron cloud, are less polarized when chemically bound, and have a greater tendency to form ionic bonds. Soft ions have lesser resistance to deformation of the electron cloud, are more polarized when chemically bound, and have a greater tendency to form covalent bonds [2–5]. In the words of Ownby and Newman [6], "The consequence of high polarizability is that the cation [metal ion] actually penetrates the anionic electron cloud [of the ligand] producing a predominantly covalent bond" (p 242). Hard metal ions bond more strongly with hard ligands (e.g., F^- and O donors), and soft metal ions bond more strongly with soft ligands (e.g., I^- and S donors) [4,7].

A modern version of metal ion classification (Leach MR. 2006. *The Chemogenesis Web Book*, http://www.meta-synthesis.com/webbook/43_hsab/HSAB.html), differing slightly from Pearson's 1963 classification, is presented here for some of the 82 ions considered in the present study: hard ions: Al^{3+}, Be^{2+}, Ca^{2+}, Ce^{3+}, Co^{3+}, Cr^{3+}, Fe^{3+}, Ga^{3+}, H^+, In^{3+}, K^+, La^{3+}, Mg^{2+}, Mn^{2+}, Na^+, Sc^{3+}, Sn^{4+}, Ti^{4+}, U^{4+}, and Zr^{4+}; borderline ions: Bi^{3+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Ir^{3+}, Ni^{2+}, Pb^{2+}, Ru^{2+}, Sn^{2+}, and Zn^{2+}; and soft ions: Ag^+, Au^+, Cd^{2+}, Cu^+, Hg^+, Hg^{2+}, Pd^{2+}, Pt^{2+}, Tl^+, and Tl^{3+}.

Toxicologists and many physiologists will recognize that the soft ions are commonly very toxic but that the hard ions of charge (Z) <3 are commonly less toxic. All ions of $Z > 2$ appear to be toxic [8]. With regard to the latter point, one must remember that multivalent cations are very prone to hydrolysis and that the free metal ion is never the majority species when $pH > pK_{H_2O}$, where pK_{H_2O} is $-\log$ of the first hydrolysis constant. For Al^{3+} that means that pH must be <5.0, and for Fe^{3+} the pH must be <2.2. This puts great restraints on toxicological studies, especially for ions injected into pH-neutral body fluids, for example, which contain numerous metal binding ligands in addition to OH^-. For studies with aquatic organisms or plant roots, simple solutions of pH <4 can be used sometimes [9,10].

The most commonly cited scale for hardness or softness is the one computed by Pearson and Mawby [11], commonly denoted by σ_P. This scale is based on ion binding to the hard ligand F^- and the soft ligand I^-. It is computed as $[CBE(F^-) - CBE(I^-)]/CBE(F^-)$, where CBE is the coordinate bond energy. This is a hardness scale because values increase with increasing hardness, but a sign change converts the scale into a softness scale. Toxicologists in particular have used this scale in their attempts to relate ion toxicity to the chemical properties of the ions [8,12–16]. It is surprising, therefore, that σ_P correlates poorly with other scales of chemical hardness or softness. Another well-known softness scale is that of Ahrland (σ_A) [17]. In the author's own words, "It is postulated that the more completely the energy spent on the formation of a positive ion in the gas phase is regained by the introduction of the ion in a hard solvent like water, the harder the ion. Thus, the larger the difference between the total ionization potential for the formation of $M^{n+}(g)$ and the dehydration energy $-\Delta H^0$ . . . , the softer the ion" (p 305). The σ_A scale correlates relatively well with other scales of chemical softness.

The last scale discussed here appears to be a favorite with physical chemists [5,18,19]. The softness scale designated here as σ_{Parr} is the reciprocal of a property referred to by its authors as absolute hardness (η). The authors of the scale [20] define hardness with these statements (pp 7512, 7513, 7516): "The

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Table 1. Sources for data and some symbols used in the article

σ_K	−Klopman's hardness scale	Klopman [31]
σ_M	Misono's softness scale	Misono et al. [32]
σ_A	Ahrland's softness scale	Jørgensen [3]
σ_Z	−Zhang's hardness scale	Zhang [33]
σ_{Parr}	1/(Parr's hardness scale)	Pearson [23]
σ_H	−Hancock's hardness scale	Hancock and Martell [34]
σ_{Kor}	1/(Komorowski's hardness scale)	Komorowski [35]
σ_P	−Pearson's hardness scale	Pearson and Mawby [11]
pK_{SP}	Solubility products of metal sulfides	Licht [36]
SLScale	Mean of normalized log K values for metal ion binding to soft ligands	Smith et al. [22]
HLScale	Mean of normalized log K values for metal ion binding to hard ligands	Smith et al. [22]
E^0	Standard electrode potentials	Vanýsek [37]
ρ_{Metal}	Bulk metal density	Winter (2007) WebElements http://www.webelements.com
χ_P	Pauling electronegativity	Barbalace (2008) EnvironmentalChemistry http://environmentalchemistry.com
I_P	First ionization potential	Barbalace (2008) EnvironmentalChemistry http://environmentalchemistry.com
T	Toxicity scales	Jones [38]; Jones [39]; McCloskey et al. [16]; Tatara et al. [15]; Lewis et al. [40]; Wolterbeek and Verburg [25]; Enache et al. [12]; Kinraide and Yermiyahu [8]; Walker et al. [13]; Workentine et al. [14]

nonchemical meaning of the word 'hardness' is resistance to deformation or change." Thus, "chemical hardness is resistance of the chemical potential to change in the number of electrons." Also, "hardness is identically one-half of the energy change for the disproportion reaction $S + S \rightarrow S^+ + S^-$." They conclude with the statement: "The hardness of a chemical species, then, is half the derivative of its chemical potential with respect to the number of electrons: $2\eta = (\delta\mu/\delta N)_Z$. There seem to be no other acceptable definitions." Hardness is computed by the formula $\eta_S = \frac{1}{2}(I_S - A_S)$, where I_S is the ionization potential and A_S is the electron affinity for S. Later, Pearson [21] noted that $2\eta = (\delta\mu/\delta N)_Z$ implies $2\eta = (\delta\mu/\delta\rho)_v$ where ρ is the electron density. Thus, η "has the meaning of resistance to change, or deformation, of the electron cloud" (p 8). Softness was defined as $1/\eta$, which I shall denote as σ_{Parr}. However satisfying σ_{Parr} may be to physical chemists, σ_{Parr} is only intermediate in its agreement with other scales of chemical softness.

I undertook the present study after noting the great disparities among the scales for hardness or softness and wondering whether it would be possible to evaluate the scales one against the other and to devise a consensus scale (σ_{Con}) for softness that was superior to any individual scale previously published. Superiority would be determined solely on the basis of correlations among published scales for softness and other possible indicators of softness, such as E^0, ρ_{Metal}, Pauling electronegativity (χ_P), metal sulfide solubilities, conformity to the hard-borderline–soft classification presented above, and so on. Finally, I was interested in the quality of the various scales as predictors (or partial predictors) of metal ion toxicity as used, for example, by Ownby and Newman [6]. Thus, the objectives of the present study were these: to evaluate the scales one against the other, to devise a superior consensus scale for softness, to evaluate the various scales as predictors of metal ion toxicity, and to relate softness and toxicity to simpler physical properties such as E^0, ρ_{Metal}, χ_P, the first ionization potential (I_P), and Z.

MATERIALS AND METHODS

Construction of σ_{Con}

Data were compiled for 92 ions. The sources for those data are presented in Table 1, and selected data are presented in Table 2. Ten scales of softness were chosen for evaluation: eight drawn from the literature (σ_K, σ_M, σ_A, σ_Z, σ_{Parr}, σ_H, σ_{Kor}, and σ_P), another consisting of the −logs of the solubility products of metal sulfides (pK_{SP}), and yet another constructed from log K values for metal ion binding to soft ligands (SLScale). Each scale was normalized by subtracting the scale mean from each number in the scale and dividing by the standard deviation. The units for each scale therefore ranged above and below 0.00, which was the mean. A scale value of −1.00 was one standard deviation below the mean, and 1.00 was one standard deviation above the mean. Finally, a consensus scale was constructed by averaging across the 10 normalized scales. The consensus scale, henceforth denoted as the observed σ_{Con} ($\sigma_{Con\ obs}$), included 51 ions, which were the number of ions for which there were three or more values from the 10 scales used in the construction.

Values for $\sigma_{Con\ obs}$ were next analyzed in terms of common physical parameters for the ions. In addition to being possibly interesting in its own right, this analysis allows for the extension of the softness scale beyond 51 ions. The analysis resulted in the equation $\sigma_{Con\ obs} = \sigma_{Con} = aE^0I_P + b\rho_{Metal}$ for which $R^2 = 0.867$, $a = 0.0607$, and $b = 0.0454$. Henceforth, $\sigma_{Con\ comp}$ will refer to values computed from the equation.

One of the 10 scales referred to previously (SLScale) was itself a composite scale also constructed by the normalization and averaging of log K values for metal ion binding to the soft ligands Cl^-, Br^-, I^-, SH^-, NH_3, thiourea, and thiosulfate. The binding constants were obtained from the National Institute of Standards and Technology [22]. The SLScale complements a scale for metal ion binding to hard ligands (HLScale; Table 2), and the HLScale is an updated version of a smaller scale published earlier [8]. For the present study, the ligand nitrilotriacetate was added to the 12 ligands used earlier. The HLScale includes 63 metal ions and H^+ based on data for the 13 hard ligands.

Assessment of $\sigma_{Con\ obs}$, $\sigma_{Con\ comp}$, and other scales

Each of the 10 softness scales (σ_K through SLScale in Table 1) was correlated with each of the nine others, and a correlation matrix of 45 R^2 values was prepared (not shown). Table 3 presents summary values in the form of means of the R^2 for the nine correlations for each scale with the others. Comparison

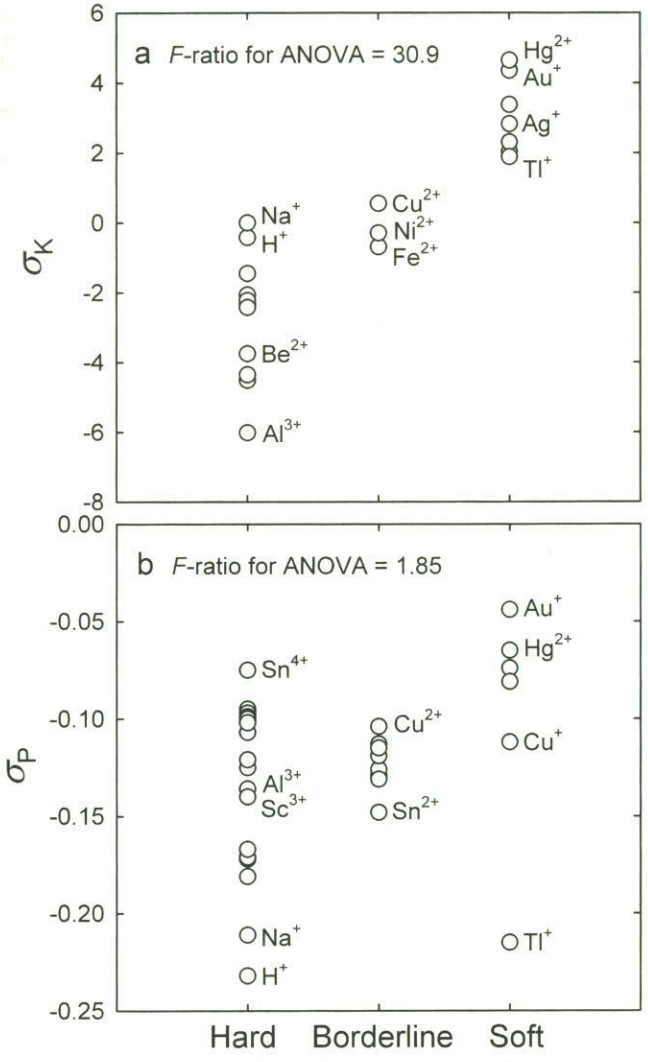

Fig. 1. Two softness scales plotted against ion classification. Agreement between the scales and the classification was evaluated by analysis of variance (ANOVA).

of the correlations was complicated by the fact that the number of ions varied for the different correlations. Thus, n varies from $n = 15$ for σ_K versus SLScale to $n = 51$ for σ_{Parr} versus σ_Z. However, the ranking of the scales (Table 3) did not change much when the set of ions was restricted to ensure a more similar suite of ions for each correlation.

The quality of the consensus scales, $\sigma_{Con\ obs}$ and $\sigma_{Con\ comp}$, was assessed by determining the correlation of each of these two with the 10 other softness scales and with the standard electrode potential (E^0), the bulk density (ρ_{Metal}), and the hard-borderline–soft classification noted in the *Introduction*. Other authors who construct or use scales for hardness or softness have also noted agreements or disagreements between the scales and the hard-borderline–soft classification [23,24]. For the present study, agreement was assessed by analysis of variance (ANOVA), and the scales were ranked according to F ratio (Table 3 and Fig. 1).

Construction of a consensus toxicity scale ($T_{Con\ obs}$)

Table 1 lists the sources of 10 published toxicity studies. The published scales were usually in the form of log concentration of metal ions required to induce 50% toxicity (death rate, inhibition of growth, and so on). These 10 scales were normalized and averaged, as in the case of the softness scales, in order to construct a consensus toxicity scale. One of the articles [25] presented a toxicity ranking based on 30 datum sets from the literature.

RESULTS

Correlation and ranking of published softness scales

The scales for softness are poorly correlated with one another (correlation matrix not shown; Table 3). In none of the 45 correlations did R^2 achieve 0.900, and in two cases $R^2 < 0.100$. For just over half the correlations, $R^2 < 0.500$. Figure 2 illustrates the poorest (Fig. 2a) and the best (Fig. 2d) correlations, and the figure presents two other correlations for the scales σ_P, σ_Z, σ_{Parr}, and σ_M. As mentioned earlier, n is variable for these correlations. For that reason the set of ions was restricted to the 23 common to all four scales in Figure 2, and the correlations were repeated. The new R^2 values are shown in the figure. Although R^2s changed somewhat, the ranking of the four correlations did not. The ranking of the 10 scales with σ_K at the top and σ_P at the bottom represents a trend that changed only slightly with further analyses (Table 3). F ratios for ANOVA for the scales versus the hard-borderline–soft classification are presented in Table 3 and Figure 1. Again, σ_K was the top-ranked scale.

Evaluation of $\sigma_{Con\ obs}$ and $\sigma_{Con\ comp}$ as softness scales

The correlation of $\sigma_{Con\ obs}$ against the 10 scales used in its construction indicates that it may be superior to any of those scales. The mean R^2 of 0.689 exceeds the value for the mean R^2 of 0.572 for σ_K, the individual scale most correlated with the others (Table 3). The scale, $\sigma_{Con\ comp}$, also appears to be superior to any of the 10 scales used to construct $\sigma_{Con\ obs}$. For the ANOVA, F ratios for $\sigma_{Con\ obs}$ and $\sigma_{Con\ comp}$ were large but ranked behind that of σ_K. Correlations of $\sigma_{Con\ obs}$ with E^0 and ρ_{Metal} ranked behind σ_A and σ_M, respectively. Figure 3 illustrates the correlations of $\sigma_{Con\ obs}$ with E^0, ρ_{Metal}, χ_P, and Z. As noted already, $\sigma_{Con\ comp} = aE^0I_P + b\rho_{Metal}$ for which $R^2 = 0.867$, $a = 0.0607$, and $b = 0.0454$, with each coefficient statistically significant.

Evaluation of the binding scale for soft ligands

The SLScale was one of the 10 scales used to construct $\sigma_{Con\ obs}$, and it has some interesting features. The SLScale correlated very well with six of the seven scales used for its construction ($R^2 = 0.808$–0.977, not shown); for log K_{NH3}, $R^2 = 0.653$. Table 3 lists $R^2 = 0.759$ for SLScale versus $\sigma_{Con\ obs}$, but a quadratic equation increased R^2 to 0.863 (Fig. 4a). Addition of Z in the equation $SLScale = a + b\sigma_{Con\ obs} + c\sigma^2_{Con\ obs} + dZ$ increased R^2 to 0.896. Finally, removal of H^+ from the regression raised R^2 to 0.922. Figure 4b illustrates that SLScale and HLScale are highly correlated for the harder ions ($R^2 = 0.853$ for ions with $\sigma_{Con\ obs} < -0.1$); all the greater outliers for the drawn line are softer ions.

Evaluation of $\sigma_{Con\ obs}$ and $\sigma_{Con\ comp}$ relative to toxicity

The 10 toxicity scales are better correlated with one another than are the softness scales (not shown). The R^2 values ranged from 0.136 to 0.898, and $R^2 > 0.500$ for 32 of the 45 correlations. Figure 5 presents some notable features of the toxicity studies. The scale most poorly correlated with all others is T_{Lewis} (Fig. 5a), and the scale best correlated with all others is $T_{McCloskey}$ (Fig. 5b). One of the scales, $T_{Kinraide}$, for root elongation, has been presented previously only in graphical form,

Table 2. List of metal ions and H^+ with the standard electrode potential (E^0), bulk density (ρ_{Metal}), first ionization potential (I_P), binding strengths to hard ligands (HLScale), binding strengths to soft ligands (SLScale), observed softness ($\sigma_{Con\ obs}$), computed softness ($\sigma_{Con\ comp}$), observed toxicity ($T_{Con\ obs}$), and computed toxicity ($T_{Con\ comp}$). For the normalization units, 0.00 is the mean, −1.00 is one standard deviation below the mean, and 1.00 is one standard deviation above the mean

Metal ion	E^0 V	ρ_{Metal} g/cm³	First I_P eV	Normalization units					
				HLScale[a]	SLScale	$\sigma_{Con\ obs}$	$\sigma_{Con\ comp}$	$T_{Con\ obs}$	$T_{Con\ comp}$
Ac^{3+}	−2.20	10.07	5.17	0.02			−0.23		0.094
Ag^{+}	0.80	10.49	7.58	−1.28	1.13	1.21	0.84	1.45	1.460
Al^{3+}	−1.66	2.70	5.99	0.67		−1.29	−0.48	−0.13[b]	−0.053
Am^{3+}	−2.05	13.67	5.99	0.26			−0.12		0.159
Au^{+}	1.69	19.30	9.22			1.78	1.82		3.065
Au^{3+}	1.50	19.30	9.22				1.72	1.14[b]	1.256
Ba^{2+}	−2.91	3.51	5.21	−1.13	−0.69	−0.63	−0.76	−0.40	−0.695
Be^{2+}	−1.85	1.85	9.32	−0.14		−1.31	−0.96	−0.66	−0.918
Bi^{3+}	0.31	9.78	7.29	1.06	0.59	0.56	0.58		0.579
Bk^{3+}		14.78	6.23	0.29					
Ca^{2+}	−2.87	1.55	6.11	−0.89	−0.60	−0.90	−0.99	−1.06	−0.955
Cd^{2+}	−0.40	8.65	8.99	−0.48	0.02	0.42	0.17	0.68	0.349
Ce^{3+}	−2.34	6.69	5.54	0.21		0.04	−0.48		−0.054
Cf^{3+}	−1.94	15.10	6.30	0.31			−0.06		0.200
Cm^{3+}	−2.04	13.51	6.02	0.28			−0.13		0.155
Co^{2+}	−0.28	8.90	7.86	−0.48	−0.27	0.08	0.27	0.12	0.458
Co^{3+}		8.90	7.86			0.06			
Cr^{2+}	−0.91	7.14	6.77	−0.36		0.21	−0.05		0.099
Cr^{3+}	−0.74	7.14	6.77	0.78		0.03	0.02	−0.14[b]	0.244
Cs^{+}	−3.03	1.88	3.89	−1.88	−0.81	−0.55	−0.63	−0.78	−0.954
Cu^{+}	0.52	8.92	7.73		0.87	0.90	0.65		1.141
Cu^{2+}	0.34	8.92	7.73	−0.09	0.88	0.41	0.57	0.92	0.787
Dy^{3+}	−2.30	8.55	5.94	0.29			−0.44		−0.028
Er^{3+}	−2.33	9.07	6.10	0.24			−0.45		−0.036
Eu^{3+}	−1.99	5.24	5.67	0.29	−0.43		−0.45		−0.033
Fe^{2+}	−0.45	7.87	7.87	−0.58		0.17	0.14	−0.12	0.316
Fe^{3+}	−0.04	7.87	7.87	1.23	−0.15	−0.15	0.34	0.58[b]	0.436
Ga^{+}	−0.20	5.90	6.00				0.20		0.398
Ga^{3+}	−0.55	5.90	6.00	0.81	−0.41	−0.16	0.07	0.22[b]	0.274
Gd^{3+}	−2.28	7.90	6.15	0.28			−0.49		−0.060
Ge^{2+}	0.24	5.32	7.90			0.17	0.36		0.554
Ge^{4+}	0.12	5.32	7.90				0.30		0.334
H^{+}	0.00		13.60	0.19	0.05	0.01		0.19[b]	
Hf^{4+}	−1.55	13.31	6.65	1.92			−0.02		0.310
Hg^{+}		13.70	10.44	0.16					
Hg^{2+}	0.85	13.70	10.44	0.86	2.78	1.34	1.16	1.86[b]	1.453
Ho^{3+}	−2.33	8.80	6.02	0.22			−0.45		−0.036
In^{+}	−0.14	7.31	5.79				0.28		0.541
In^{3+}	−0.34	7.31	5.79	0.69	0.59	0.27	0.21	0.48[b]	0.360
Ir^{3+}	1.16	24.65	9.10			1.74	1.76		1.281
K^{+}	−2.93	0.86	4.34	−1.75	−0.90	−0.87	−0.73	−1.19	−1.124
La^{3+}	−2.38	6.15	5.58	0.18		−0.78	−0.53	0.30	−0.081
Li^{+}	−3.04	0.54	5.39	−1.57		−1.47	−0.97	−1.25	−1.512
Lu^{3+}	−2.28	9.84	5.43	0.28		−0.47	−0.30		0.052
Mg^{2+}	−2.37	1.74	7.65	−0.88	−0.68	−0.99	−1.02	−1.08	−0.986
Mn^{2+}	−1.18	7.47	7.44	−0.62	−0.61	0.16	−0.20	−0.35	−0.063
Mn^{3+}		7.47	7.44	1.73		0.09			
Mo^{3+}	−0.20	10.28	7.10				0.38		0.460
Na^{+}	−2.71	0.97	5.14	−1.71	−1.10	−0.97	−0.80	−1.40	−1.235
Nd^{3+}	−2.32	6.80	5.53	0.25			−0.47		−0.047
Ni^{2+}	−0.26	8.91	7.64	−0.41	−0.38	0.07	0.29	0.31	0.474
Ni^{3+}		8.91	7.64			0.06			
Np^{4+}		20.45	6.19	1.61					
Pb^{2+}	−0.126	11.34	7.42	−0.20	−0.18	0.56	0.46	0.074	0.667
Pd^{2+}	0.951	12.02	8.34	0.59	1.88	1.25	1.03		1.303
Pm^{3+}	−2.30	7.26	5.55	0.25			−0.45		−0.032
Pr^{3+}	−2.35	6.64	5.46	0.16			−0.48		−0.052
Pt^{2+}	1.18	21.09	9.00		1.63	1.17	1.60		1.945
Pu^{3+}	−2.03	19.82	6.06	0.11			0.15		0.324
Pu^{4+}		19.82	6.06	1.89					
Rb^{+}	−2.98	1.53	4.18	−1.80		−0.72	−0.69		−1.046
Ru^{2+}	0.46	12.37	7.37				0.77		1.010
Sc^{3+}	−2.08	2.98	6.54	0.88		−0.78	−0.69	−0.19[b]	−0.177
Sm^{3+}	−2.30	7.35	5.64	0.22			−0.45		−0.038
Sn^{2+}	−0.14	7.31	7.34	0.57	−0.30	0.10	0.27		0.458
Sn^{4+}		7.31	7.34			0.43			
Sr^{2+}	−2.90	2.63	5.70	−1.01	−0.73	−0.74	−0.88	−1.07	−0.830
Tb^{3+}	−2.28	8.22	5.86	0.22			−0.44		−0.028
Th^{4+}	−1.90	11.72	6.08	1.54			−0.17		0.299

Table 2. Continued

Metal ion	E^0 V	ρ_{Metal} g/cm^3	First I_P eV	Normalization units					
				HLScale[a]	SLScale	$\sigma_{Con\ obs}$	$\sigma_{Con\ comp}$	$T_{Con\ obs}$	$T_{Con\ comp}$
Ti^{2+}	−1.63	4.51	6.82			0.27	−0.47		−0.370
Ti^{3+}	−1.37	4.51	6.82			0.04	−0.36		0.017
Ti^{4+}		4.51	6.82			−0.79			
Tl^{+}	−0.34	11.85	6.11	−1.50	−0.57	0.28	0.41	0.72	0.755
Tl^{3+}	0.74	11.85	6.11	1.90		0.69	0.81		0.718
Tm^{3+}	−2.32	9.32	6.18	0.34			−0.45		−0.033
U^{4+}		18.95	6.05	1.83	−0.14				
V^{2+}	−1.18	6.11	6.74			0.32	−0.20		−0.072
V^{3+}		6.11	6.74	0.83		0.14			
Y^{3+}	−2.37	4.47	6.38	0.30		−0.83	−0.72	−0.33	−0.193
Yb^{3+}	−2.19	6.57	6.25	0.36			−0.53		−0.084
Zn^{2+}	−0.73	7.14	9.39	−0.41	−0.52	−0.02	−0.09	0.36	0.052
Zr^{4+}	−1.45	6.51	6.84	1.99			−0.31		0.288

[a] Use the formula log K_{PM} = 3.00 + 1.75HLScale to compute log K of metal ion binding constants to plasma membranes (R^2 = 0.995 for observed log K versus HLScale [8]).

[b] The toxicity of these readily hydrolyzed ions ($pK_{H_2O} \leq 5$) may be underestimated in some studies, or it may be overestimated if greatly intoxicating polyvalent cations (e.g., $AlO_4Al_{12}(OH)_{24}(H_2O)_{12}^{7+}$) appear.

and an additional ion, Tb^{3+}, has been evaluated. Therefore, $T_{Kinraide}$ is presented here in the form of −log of the ion activity at the plasma membrane surface required to reduce root elongation 50%: Ag^+, 6.0; Al^{3+}, 5.1; Ba^{2+}, 1.7; Be^{2+}, 2.7; Ca^{2+}, 1.8; Cd^{2+}, 3.9; Co^{2+}, 3.7; Cu^{2+}, 5.7; H^+, 3.8; K^+, 0.8; La^{4+}, 4.4; Mg^{2+}, 1.9; Na^+, 0.7; Ni^{2+}, 3.8; Pb^{2+}, 3.6; Sc^{3+}, 5.9; Sr^{2+}, 1.8; Tb^{3+}, 4.3; Tl^+, 3.6; and Zn^{2+}, 3.7. References to the computation of plasma membrane surface activities and toxicities are presented in previous reports [8,26,27]. The toxicities of Al^{3+} and Sc^{3+} were greater in that study than in some others because of the attention given to speciation as described later.

It was noted previously that hard ions with $Z < 3$ are generally not toxic but that all ions with $Z > 2$ generally are toxic. Figures 5c and 5d present ion toxicity as a function of charge

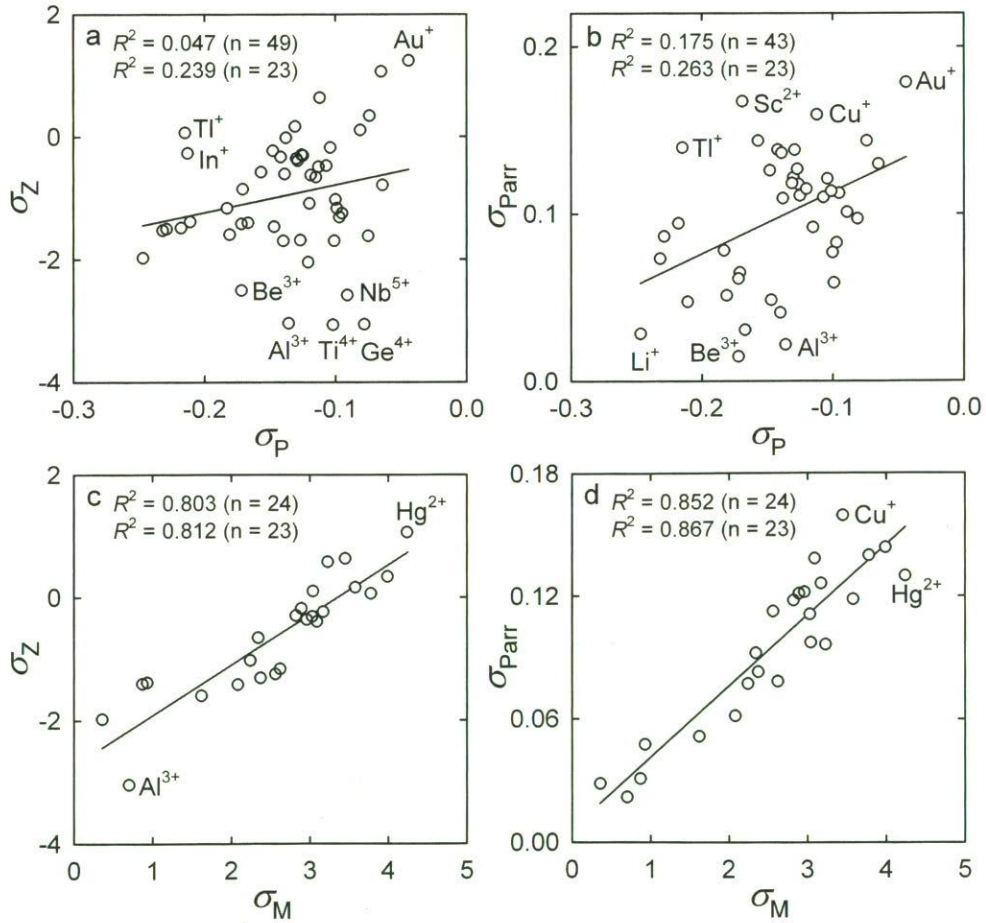

Fig. 2. Some softness scales plotted one against the other. The smallest of the 45 correlations was for σ_Z versus σ_P, and the greatest was for σ_{Parr} versus σ_M.

Table 3. Linear correlations among various scales. The first number column presents the mean R^2 values for correlations of the indicated scale versus the nine other scales from the 10 scales σ_K through σ_P. Subsequent columns present the R^2 values for the correlations between the two scales or parameters indicated. *F* ratio refers to the analysis of variance for the indicated scale versus the hard-borderline–soft classification

All softness scales		E^0	σ_{Metal}	*F* ratio	$\sigma_{Con\ obs}$	$\sigma_{Con\ comp}$	$T_{Con\ obs}$
σ_K	0.572	0.508	0.574	30.9	0.715	0.609	0.333
σ_M	0.553	0.627	0.821	14.9	0.862	0.716	0.662
σ_A	0.505	0.819	0.730	12.0	0.805	0.839	0.773
σ_Z	0.500	0.417	0.293	15.9	0.733	0.584	0.532
σ_{Parr}	0.467	0.380	0.260	9.1	0.728	0.495	0.462
SLScale	0.448	0.603	0.434	8.7	0.759	0.698	0.655
σ_H	0.442	0.628	0.411	14.8	0.715	0.694	0.544
pK_{SP}	0.395	0.440	0.571	1.7	0.565	0.542	0.477
σ_{Kor}	0.377	0.286	0.412	4.9	0.508	0.401	0.293
σ_P	0.332	0.451	0.420	1.8	0.500	0.398	0.592
$\sigma_{Con\ obs}$	0.689[a]	0.780	0.755	23.0	1.000	0.867	0.734
$\sigma_{Con\ comp}$	0.598[b]	0.873	0.636	25.3	0.867	1.000	0.807

[a] Mean R^2 for correlation of $\sigma_{Con\ obs}$ versus the 10 scales σ_K through σ_P (mean of fifth number column, values 0.715–0.500).
[b] Mean R^2 for correlations of $\sigma_{Con\ comp}$ versus the 10 scales σ_K through σ_P (mean of sixth number column, values 0.609–0.398).

for harder ions ($\sigma_{Con\ obs} < -0.1$) and for softer ions ($\sigma_{Con\ obs} \geq -0.1$). Therefore, $T_{Con\ obs}$ appears to be a function of softness and charge, and for the equation $T_{Con\ obs} = a\sigma_{Con\ comp} + b\sigma_{Con\ comp}Z + cZ$, $R^2 = 0.923$, $a = 2.16$, $b = -0.521$, and $c = 0.0778$, with all coefficients statistically significant. This equation indicates an interaction between softness and charge, and this interaction is illustrated in Figure 6, where the slope of plots for $T_{Con\ obs}$ versus $\sigma_{Con\ comp}$ can be seen to decrease with increasing charge. The inset figure in Figure 6 presents the correlation for $T_{Con\ obs}$ versus $T_{Con\ comp}$, the latter as computed by the equation just given.

DISCUSSION

The objectives of the study appear to have been achieved. Hardness and softness scales were objectively ranked, and a consensus scale for softness ($\sigma_{Con\ obs}$) was devised that is superior to previously published scales. Superiority was determined on the basis of correlations among published scales for

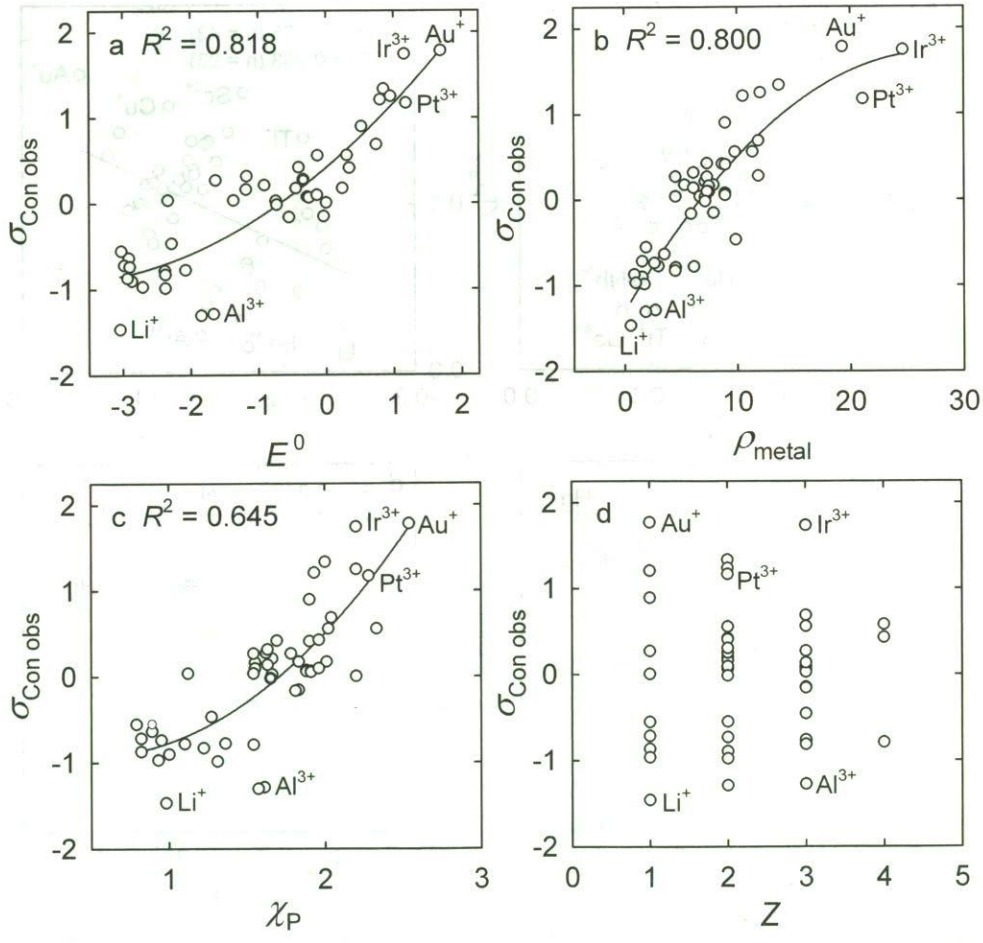

Fig. 3. The consensus scale for ion softness ($\sigma_{Con\ obs}$) plotted against physical parameters of the metals.

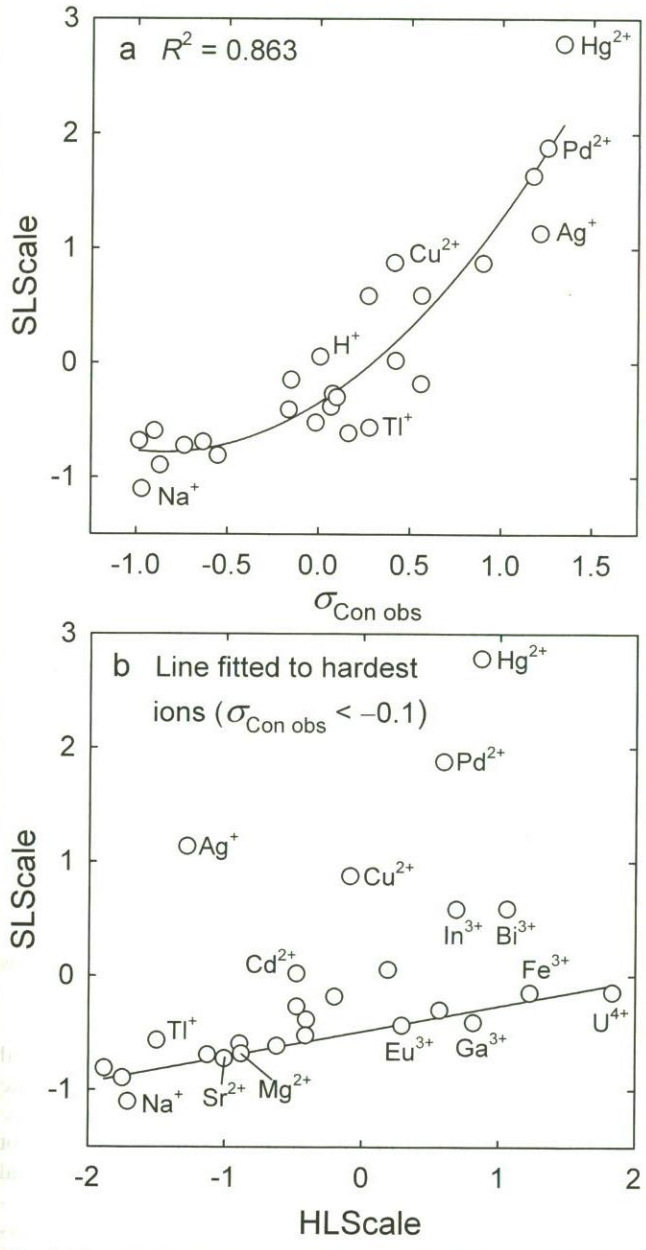

Fig. 4. The consensus scale for ion binding to soft ligands (SLScale) plotted against $\sigma_{Con\ obs}$ and against the consensus scale for ion binding to hard ligands (HLScale).

softness and other possible indicators of softness, such as E^0, ρ_{Metal}, χ_P, conformity to the hard-borderline–soft classification, and so on. Because of the great disagreement among the scales, one must wonder how the 10 scales used in the construction of $\sigma_{Con\ obs}$ were selected. Principally, scales were selected on the basis of their use (citation in the literature). No commonly used scale was deliberately omitted because of apparent incompatibility with other scales or presumed inaccuracy. Interestingly, the most widely used scale (σ_P) was the one ranked 10th among the 10 scales (Table 3). Certainly some other scales are available. Among them are three scales presented by Martin [24]. Two of those scales have a middling correlation with other scales, and one correlates poorly.

Eventually, any scale must conform to what I have referred to as chemical lore, and other authors appear to agree. Despite the statement of Parr and Pearson [20] that "there seem to be no other acceptable definitions [of hardness other than $\eta = (\delta\mu/\delta N)_Z/2$ or $\eta_S = (I_S - A_S)/2$]" (p 7516), Pearson [23] later thought it "necessary to show that $(I - A)$ indeed does correlate with earlier assignments of hardness and softness for various systems" (p 736). He also stated, "It can be seen that . . . the values of η calculated for these ions agree very well with their known chemical hardness." However, the scale σ_{Parr}, based on $1/\eta_S = 2/(I_S - A_S)$, exhibits only a modest agreement with "earlier" or "known" assignments of chemical hardness or softness, as demonstrated in Table 3. Martin [24], in reference to his scales, stated, "These scales probably correspond to what most investigators imply when they use the terms hardness and softness" (p 27). However, his three scales agree poorly with one another (R^2s were 0.538, 0.127, and 0.125). Thus, the present study has done what previous authors have attempted to do either theoretically or empirically: Incorporate into a quantitative scale the accumulated lore regarding chemical softness or hardness. This was done by deriving from 10 existing scales a consensus scale for softness. Then the consensus scale was evaluated against the scales used in its construction and against other measures of softness not used in the construction.

It is well known that soft, or class B, metal ions are often very toxic [8,28]. Thus, two of the objectives of the study were to evaluate various softness scales as predictors of metal ion toxicity and to relate concepts such as softness and toxicity to simpler physical properties such as E^0, ρ_{Metal}, I_P, χ_P, and Z. The finding with regard to the first of these additional objectives is that only σ_A and pK_{SP} compare well with $\sigma_{Con\ obs}$ and $\sigma_{Con\ comp}$ as indicators of toxicity ($R^2 = 0.874$ for $T_{Con\ obs} = a + b\sigma_A + c\sigma_A Z + dZ$ and $R^2 = 0.832$ for $T_{Con\ obs} = a + bpK_{SP} + cpK_{SP}Z + dZ$). The second of the additional objectives is met with equations that relate softness to E^0, ρ_{Metal}, and I_P, and relate toxicity to softness and Z:

$$\sigma_{Con\ obs} = aE^0 I_P + b\rho_{Metal} \quad (1)$$

$$T_{Con\ obs} = a\sigma_{Con\ comp} + b\sigma_{Con\ comp}Z + cZ \quad (2)$$

where $R^2 = 0.867$, $a = 0.0607$, and $b = 0.0454$ for Equation 1 and $R^2 = 0.923$, $a = 2.16$, $b = -0.521$, and $c = 0.0778$ for Equation 2.

Although Equation 2 predicts toxicity well, it is not certain that charge influences toxicity directly. Toxicity is also related to strength of binding to biomass (plasma membranes, cell walls, proteins, and so on [8]), and strength of binding is related to charge. Consider these facts: The strength of metal ion binding to biomass is similar to binding to hard ligands (HLScale) [8]. Some but not all ions of small HLScale are nontoxic, but all ions of large HLScale are toxic (Fig. 8a in Kinraide et al. [8] and read Fig. 4b in conjunction with Table 2). The binding strength of harder metal ions ($\sigma_{Con\ obs} < -.1$) to hard ligands is influenced by charge ($R^2 = 0.916$ for HLScale $= a + bZ^2$), the binding strength of harder metal ions to soft ligands is influenced by charge ($R^2 = 0.854$ for SLScale $= a + bZ^2$), the binding strength of softer metal ions ($\sigma_{Con\ obs} \geq -.1$) to hard ligands is modestly influenced by charge ($R^2 = 0.585$ for HLScale $= a + bZ^2$), but the binding strength of softer metal ions to soft ligands is not influenced by charge ($R^2 = 0.004$). Charge appears to influence the toxicity of harder ions (Fig. 5c) but not softer ions (Fig. 5d), but, as just noted, these effects are not independent of binding strength.

Is there any evidence that charge is an independent determinant of toxicity? The rhizotoxicity of Al species provides

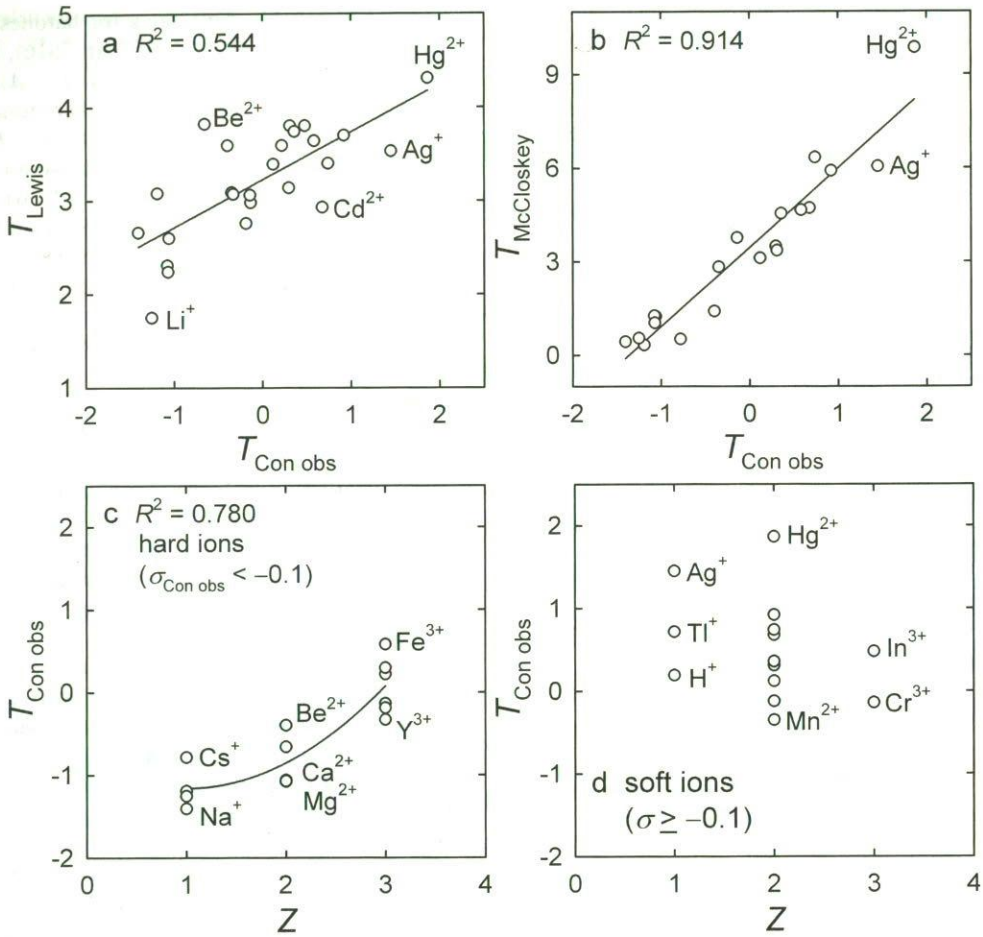

Fig. 5. The consensus scale for ion toxicity ($T_{Cons\ obs}$) plotted against two published scales (T_{Lewis} and $T_{McCloskey}$) and against charge (Z). Figures (**a**) and (**b**) present the smallest and greatest correlations, respectively, for individual scales versus $T_{Cons\ obs}$.

circumstantial but inconclusive evidence. Intoxicating effectiveness follows the order $AlO_4Al_{12}(OH)_{24}(H_2O)_{12}^{7+} > Al^{3+} > AlF^{2+} > AlF_2^+$, but this may also be the order of binding strength to cell surfaces. (The tested hydroxo-, sulfato-, organo-, and phosphato-Al species are not rhizotoxic at achievable concentrations [29].) Other polyvalent cations, such as poly-L-lysine, are toxic [30]. The discovery of a highly charged, intoxicating cation that otherwise had the characteristics of nonintoxicating ions (hard and weakly binding) would be interesting because the only characteristic predisposing the ion to toxicity would be charge. I have not found such an ion among the metals. Similarly interesting is Ag^+ because its only predisposition for toxicity is softness and not charge or strength of binding [8] (Fig. 4b).

How might softness determine toxicity? The biotic ligand model proposes that an intoxicating ion must first bind to a cell-surface ligand [27]. The actual intoxication need not occur at that site, but occupation of that site must be related to the intoxication that may occur intracellularly. The connection to softness may be that the biotic ligand is soft—perhaps a thiol- or sulfhydryl-bearing protein [28]. Perhaps we could name this extended model the soft biotic ligand model (SBLM). If the SBLM accounts for most metal ion toxicity, then we might expect SLScale to predict toxicity better than softness itself. In fact, equations of the form $T_{Con\ obs} = f(\text{SLScale}, Z)$ predict toxicity fairly well but not as well as $T_{Con\ obs} = a\sigma_{Con\ comp} + b\sigma_{Con\ comp}Z + cZ$.

I consider the SBLM to be a likely mechanism, but the data are presently inadequate to resolve the issue. Of course, an SBLM may apply to some of the metal ions but not all, and the mechanism will probably be determined only when some likely ligands have been identified and then altered by genetic modification from soft to hard. If such an alteration were not lethal and if the alteration reduced the sensitivity to soft metal ions, then the SBLM would be supported. A search for Ag^+-resistant mutants may be worthwhile because Ag^+ binds weakly to hard ligands and to most biomass (Table 2) but is extremely toxic. Perhaps the unmutated ligand binds Ag^+ strongly, but the mutated ligand binds Ag^+ weakly, indicating a possible transformation from soft to hard.

In some toxicological studies the speciation of ions is difficult to determine and may have been neglected. This can lead to the misattribution of toxicity to one ion when another may be the toxicant. In the scale of Kinraide and Yermiyahu [8] and presented in the *Results* section as $T_{Kinraide}$, great care was taken to ensure that in the Al studies, for example, all species other than Al^{3+} were excluded or accounted for. Surely, the injection of $AlCl_3$ solutions into the bloodstream, for example, would not allow the attribution of toxicity specifically to the Al^{3+} species, and in some cases, as with Fe, Cr, or Mn, for example, oxidation or reduction may lead to misattribution of toxicity. Thus, the injection of $FeCl_3$ into the bloodstream could result in several Fe(III) and Fe(II) species but virtually no Fe^{3+}.

In conclusion, improved scales for metal ion softness and toxicity have been constructed from previous scales. Softness can also be computed from three physical parameters (E^0, I_P, and ρ_{Metal}) by a simple equation (Eqn. 1), and toxicity can be

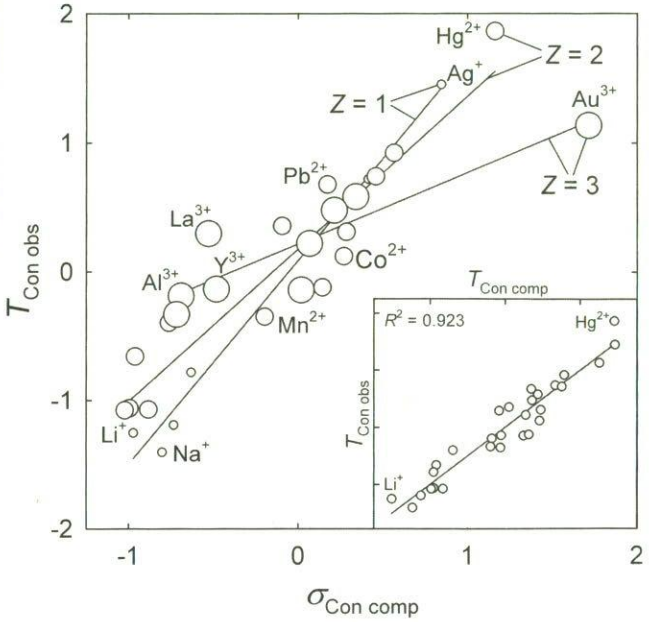

Fig. 6. The consensus scale for ion toxicity ($T_{\text{Cons obs}}$) plotted against ion softness computed as $\sigma_{\text{Con comp}} = aE^0I_P + b\rho_{\text{Metal}}$. The lines are fitted to ions of charge 1, 2, or 3. The inset presents a plot of observed versus computed toxicity ($T_{\text{Con comp}} = a\sigma_{\text{Con comp}} + b\sigma_{\text{Con comp}}Z + cZ$).

computed from softness and charge (Eqn. 2). The mechanisms of toxicity are very poorly understood for most ions. The fact that ions are toxic if they are soft or highly positively charged may guide the search for possible cell-surface ligands whose occupancy may initiate intoxication.

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